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North Carolina Univ. at Chapel Hill

Prepared for

Health Effects Research Lab.
Research Triangle Park

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16. ABSTRACT

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3. Perform collaborative research in areas relevant to EPA's mission, especially in the air program; but also in other areas (e.g., neurotoxicology, indoor air).
4. Undertake research that could not be readily accomplished by EPA with its existing personnel — both in the area of development and application of techniques, and in the performance of research.
5. To provide access to diseased as well as normal human subjects, including children, in order to study "sensitive" as well as "normal" populations challenged with inhaled pollutants in highly controlled environmental exposure chambers.

This paper has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for presentation and publication.

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U.S. EPA Cooperative Agreement

with the University of North Carolina at Chapel Hill

Center for Environmental Medicine

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CR 807392

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INTRODUCTION

This final report is designed as an overview of more than five years of collaborative work under the auspices of a general cooperative agreement between EPA and UNC-CH. Detailed interim progress reports were submitted in 1982 and 1984 in relation to continuation applications. Quarterly reports have also been regularly submitted to the project officer.

In addition, our 1985 application for the current agreement (Cooperative Agreement, CR 812738) incorporated a detailed summary of accomplishments under the Agreement which is the subject of the present report.

In the present report, the major elements are:

1. Research in support of EPA goals:
    a. scientific reports and papers arranged by year from 1981-1985 in Appendix 1.
    b. equipment purchased to support research (Appendix 2).
    c. space acquisition and renovation
    d. impact of the science on EPA's regulatory mission
    e. recruitment of able scientists
2. Other benefits:
    a. new research techniques
    b. new research directions
    c. training experience for young investigators for both EPA and UNC (Appendix 3)
    d. enrichment of the scientific milieu (Appendix 4)
    e. access of EPA to UNC resources and vice versa

A closing financial summary has been submitted separately by the UNC Office of Contracts and Grants.

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At the same time, the University recognized the importance of EPA's (HERL) research program to its own mission, and benefitted from the access of University faculty to the HERL scientific staff, to EPA research facilities, and to EPA funding support.

At the inception of the Cooperative Agreement in 1980, it was generally recognized that an immediate priority was the publication of significant peer-reviewed research, relevant to EPA's mission, involving HERL scientists at the Clinical Branch of the Inhalation Toxicology Division located on the UNC medical campus in Chapel Hill. Major attention was focussed on the "criteria" pollutant gases -- O_3, NO_2, SO_2 and CO, and to particulate-gas interactions. Furthermore, the research was conducted almost exclusively with human subjects because of the immediate applicability of such research to the development and justification of national air quality standards.

Initially, the research was performed using well-established testing procedures which focussed on pollutant inhalation-induced changes in lung physiology. Very quickly however, new types of testing procedures were developed and introduced into the repertoire of the Clinical Studies Branch operation (Bromberg et al, 1981; Pimmel et al, 1981). Furthermore, effects of exposure to air pollution <u>other</u> than changes in respiratory mechanics were systematically investigated. These included studies of respiratory epithelial function, assessment of inflammatory changes in the airways, and evaluation of the effects of criteria pollutants on pulmonary alveolar macrophages and on pulmonary vasculature (Knowles et al, 1981; Carson et al, 1982; Hu et al, 1982; Friedman et al, 1983 and 1985; Bromberg et al, 1984; Carson et al, 1985).

In order to perform such studies in human subjects, the technique of bronchoalveolar lavage using fiberoptic bronchoscopy was established in the laboratories of the Clinical Research Branch. <u>In vitro</u> culture of lung cells

and airways epithelial cells was also developed in order to be able to extend animal studies to human tissue (Wu et al, 1985). Finally, animal models were employed to gain insight into mechanisms underlying pollutant effects (Henry and Ranga, 1983; Range et al, 1983; Bromberg et al, 1984). These efforts have led to collaboration with the Toxicology Branch, ITD and interaction with HERL's "extrapolation modelling" initiative.

The success of the Cooperative Agreement can be gauged in several ways:

1. Publications record in peer-reviewed journals. See Appendix I.
2. Publication of work from the Clinical Research Branch which has had significant impact on the regulatory process.
3. Evidence of leadership in keeping inhalation toxicology and air pollution research in step with the advances in modern scientific research, especially as they apply to lung biology.
4. Evidence of ability to recruit and retain productive scientists.
5. Training in inhalational toxicology.

In 1980 our understanding of the effects of controlled exposures of human subjects to the various criteria pollutants was as follows:

1. Ozone - Effects of controlled exposures were difficult to demonstrate at inhaled concentrations less than 0.3 ppm. (Primary standard set at 0.08 ppm based largely on field observations). Little solid information on effects in well-defined, potentially susceptible populations such as patients with asthma, patients with irreversible chronic obstructive lung disease, and children. Epidemiologic studies suggested a possible increase in respiratory infections related to ozone exposure.

2. NO_2 - No effects in normal individuals after exposure to <1 ppm (Primary standard set at 0.053 ppm). However a publication in 1976 claimed that

after exposure to only 0.1 ppm NO_2, asthmatic subjects developed increased bronchial reactivity to challenge with aerosolized bronchoconstrictor chemicals.

3. CO - No cardiovascular effects in normal individuals of blood carboxyhemoglobin (COHb) levels of 5% or less. However, in patients with ischemic heart disease, effects were claimed at levels as low as 2% COHb. As in the case of NO_2 effects in asthmatic subjects, the understanding of COHb effects in subjects with ischemic heart disease was based principally on work from the laboratory of one individual.

Furthermore, there appeared to be significant uncertainty about the quantitative relation between ambient (inspired) CO concentration and changes in blood COHb levels in normal and diseased individuals under various exposure conditions. This was true despite the existence of an equation developed by Coburn, Forster and Kane in 1965, that related the time course of changes in blood COHb level to inspired CO concentration and to several physiological variables that would characterize the individual subjects exposed to ambient CO.

4. SO_2 - Despite substantial evidence from field studies linking SO_2 (and particulates) to serious respiratory health effects of air pollution, including various air pollution "disasters", controlled environmental chamber studies in normal subjects had failed to reveal measureable respiratory effects of SO_2 levels as high as 3 ppm. The ambient air quality standard was 0.14 ppm, (24 hr average), however.

The Cooperative Agreement with the UNC CEM has provided important support to the following examples of published collaborative work with the CRB which have had a major impact on our understanding of the quantitative aspects of health effects of exposure to the criteria air pollutants:

1. Ozone:

It is now clearly established that adult normal subjects develop

symptoms and impaired pulmonary function following exposure to as little as 0.12 ppm O_3, provided that the subjects perform exercise during the exposure so as to increase their ventilation (McDonnell et al, 1983). Normal children, 8-11 years old, are similarly susceptible to ozone (McDonnell et al, 1985). These changes are not dependent on bronchoconstriction which appears to be a relatively minor effect of O_3 inhalation. They are due to an involuntary inhibition of deep inspiration, probably neurally mediated (Hazucha, Bates, Bromberg, in preparation). There is enormous intersubject variability in the intensity of the response to O_3. This variability is <u>not</u> attributable to a lack of reproducibility of the O_3 effect in a given subject. Nor does it appear to be attributable to age, sex, race or atopic status. The reasons for extreme variability of individual susceptibility among normal individuals remain to be elucidated and this problem constitutes an element of our present research program. One possibility is that ozone uptake by the respiratory tract differs from one individual to another. Indeed, evidence for substantial inter-subject variability of nasopharyngeal uptake of ozone has recently been obtained by Gerrity and O'Neil. Another possibility is the existence of biological differences in the neural elements subserving ozone-induced effects on airways sensation.

Patients with chronic, irreversible, obstructive lung disease are not highly sensitive to respiratory effects of ozone (Solic et al, 1982; Kehrl et al, 1983 and 1985). Patients with mild asthma are probably not especially sensitive to ozone inhalation.

Concurrent exposure to ozone and low concentrations (100 $\mu g/m^3$) of acid sulfate aerosols does not markedly enhance the ozone effect in normal subjects, although there is a trend in that direction (Stacy, et al, 1981). These possible interactions between O_3 and acid sulfate exposure need further exploration, particularly in subjects with reactive airways diseases.

We have shown that O_3 inhalation causes inflammation in human airways (Graham et al, 1985). Ozone exposure also acutely increases respiratory epithelial permeability in human subjects (Kehrl et al, 1987 in press). These studies are particularly important for two reasons:

1. They provide a basis for correlating animal and human toxicology.

2. They provide a basis for making judgments as to the relevance to health of the acute reversible changes in lung function provoked by controlled ozone exposure in environmental chamber studies.

Investigations in other biological systems of the mechanisms of ozone effects are critical to regulatory decision-making for similar reasons. Thus, we have shown that endothelial cells (in culture) lose their ability to produce prostacyclin from arachidonate-containing membrane lipids after a brief exposure to ozone (Friedman et al, 1985). This effect appears to be due to specific inhibition of cyclooxygenase activity by a peroxide-dependent mechanism. Endothelial cells do not have vigorous anti-oxidant mechanisms and are particularly vulnerable to oxidant injury.

The physiological relevance of these _in vitro_ findings is supported by the observation that following ozone exposure, the canine pulmonary vasculature _in vivo_ exhibits enhanced susceptibility to vasoconstrictive stimuli. Similar effects are observed when prostacycline synthesis is specifically inhibited by pretreatment with the cyclooxygenase blocker, indomethacin (Friedman et al, 1985).

The pulmonary alveolar macrophage is much more resistant to oxidant injury and displays a different repertoire of arachidonate metabolism than endothelial cells. Nevertheless, there appear to be major new lipid oxidation products as well as changes in arachidonate liberation and metabolism patterns when cultured pulmonary alveolar macrophages are exposed to ozone _in vitro_. Among other things, we hope to use this information to estimate the levels of

ozone in the alveolar regions of the lung parenchyma during exposure to this gas. Possible effects of ozone exposure of macrophages on their immunological function, microbicidal properties, and production of monokines are also under investigation. A variety of assays of specific elements of cellular activity relevant to these activities have been put in place to further pursue these questions.

Because epithelial cells are directly exposed to reactive inhaled gases, we have made a special effort to develop effective methods to culture and study respiratory epithelial cells, including human airway cells. The basic techniques were learned from Professor Reen Wu who spent three months with the Center in late 1982, supported by the Cooperative Agreement.

There is a large amount of evidence to indicate that ozone damages or modifies respiratory epithelial function. Thus, epithelial permeability to polar solutes is increased, active ion transport is increased, mucin secretion from surface epithelial cells occurs, inflammatory cells infiltrate the epithelium and appear on the airway surface, ciliated cells are damaged and alveolar type 1 lining cells are damaged. The epithelium has a number of important protective functions such as mucociliary clearance of inhaled particulates, killing of inhaled microbes, maintenance of a thin layer of airways surface liquid with suitable viscoelastic properties and secretion of macromolecules (e.g., the surfactant of the alveolar type 2 cells, the 10,000 dalton Clara cell protein, antibodies, etc). These functions are essential to the long term maintenance of respiratory health.

We studied twenty-four young adult male volunteers experimentally inoculated with type 39 rhinovirus to determine whether the course of viral infection was modified by exposure to moderate levels of ozone (0.3 ppm for 6 hours a day) over the five days following virus inoculation (Henderson et al, 1983). No differences in rhinovirus titers in nasal secretions, recruitment of neutrophils

into nasal secretions, levels of interferon in nasal lavage fluid, in vitro lymphocyte proliferative responses to rhinovirus antigen, or levels of convalescent serum neutralizing antibody to type 39 rhinovirus were demonstrated in relation to ozone exposure. The level and pattern of ozone exposure used in this experiment had no demonstrable adverse effects on the immune responses necessary to limit and terminate rhinovirus infection of the upper respiratory tract. Thus, in this unique study we have not been able to demonstrate any effect of significant O_3 exposure on the development or course of a common rhinovirus upper respiratory infection. This finding does not however preclude the possibility that infections caused by other agents might be affected by O_3 exposure, or that a different sequence of viral infection and ozone exposure might produce a different outcome in the series of measurements made.

In addition to these vital functions, the epithelium is the tissue of origin of primary lung cancers. Oxidant substances can act as tumor promoting agents and as DNA-damaging substances. We therefore have developed our epithelial cell culture facilities not only to examine the effect of oxidant exposures on various protective functions but also to be able in the future to examine the possible role of oxidant gas exposures in mechanisms of tumor promotion.

Indeed, there is increasing concern for the possible health effects of a large number of inhaled chemicals other than the criteria pollutants. EPA has taken an increasingly important role in developing regulatory guidelines for air toxics including volatile organic compounds, sidestream tobacco smoke, and indoor air pollution. In vitro systems using cultured human lung cells will be essential to pursuing this work.

2. NO_2

In a carefully designed effort to repeat the 1976 study of Orehek et al

that claimed enhanced bronchial reactivity in asthmatic subjects following exposure to 0.1 ppm NO_2, we were unable to confirm this finding (Hazucha et al, 1983). Newly designed methodology was employed in this study, both to assess the airways response and to provide quantitative exposures to inhaled aerosolized bronchoconstrictors. These techniques have been incorporated into the CRB's standard lung function testing procedures.

More recently, the CRB group as well as others have been re-examining the question of NO_2 effects in asthmatics using higher NO_2 levels (up to 0.6 ppm) and incorporating exercise into the exposure protocols. Some evidence of effects of exposure to 0.3 ppm NO_2 has been obtained, but the reproducibility of these observations is not established. Nevertheless, these findings suggest that the potential toxicity of NO_2 for susceptible human subjects requires considerably more attention. Studies of epithelial function in animal models and in cultured cell systems will also be needed. The potential tumor promoting actions of NO_2 also require consideration.

3. CO

Our contributions have been in three major areas:

a. We have provided evidence to support the use of the Coburn equation to infer the relation between inspired CO concentrations and the level of blood COHb (Hazucha et al, 1984). This will be critical to the ultimate "translation" of health effects attributable to COHb into an ambient air quality standard.

b. We have developed a system for transient exposures of subjects to very high CO levels. We are using this system to study possible neurotoxic effects and to look for significant deviations of COHb kinetics from the Coburn equation under these extreme conditions. This work is relevant to EPA which has entered into an agreement with the Department of the Army to pursue these

problems in inhalation toxicology.

c. We have performed detailed studies of the effects of approximately 4% COHb and 6% COHb on myocardial function in patients with criteria for the presence of ischemic heart disease (Sheps et al, 1987, in press; Adams et al, 1987, submitted). We used angina, ECG changes, and ventricular function as determined by gamma camera imaging as the dependent variables. The studies were carried out in double-blind fashion in the CRB laboratories by a UNC-CRB team led by David Sheps MD, Associate Professor of Medicine (Cardiology). No changes were demonstrable at a 3.8% COHb level. Preliminary analysis suggests, however, that evidence of enhanced ischemia during exercise will be shown at the ~ 6% COHb level.

The possibility of COHb-induced arrhythmias is also being studied in patients with heart disease. The study of defined subpopulations of patients with ischemic heart disease and of patients with other forms of heart disease is projected.

Dr. Sheps was also a member of the scientific review group that reviewed the work of Professor Aronow on COHb effect on patients with ischemic heart disease, and reported its findings and recommendations to US EPA. The substantive questions raised by this review has made it imperative to develop a new body of evidence pertinent to this difficult regulatory area.

We have also pointed out that as the scientific evidence relating COHb levels to adverse health effects in susceptible populations accumulates, we should not neglect the practical problem of translating COHb levels into ambient air quality criteria for CO. Basing this work on the Coburn equation should allow us to be prepared to come forward with specific air quality criteria as soon as the maximum acceptable COHb level is agreed upon.

4. SO_2. We have contributed to the recently-acquired, but now

solid body of evidence showing that mild asthmatics are extraordinarily susceptible to bronchospasm during exercise in atmospheres containing as little as 0.25 ppm SO_2. The mechanisms underlying this interaction between SO_2 and exercise are not yet clear. Nor has the potential relation between ingested sulfite sensitivity and inhaled SO_2 reactivity been clarified. The mechanisms of SO_2-induced bronchoconstriction appear to involve cholinergic mechanisms but also may involve chemical mediators, mast cells, and possibly neural mechanisms.

Interactions between O_3 and SO_2 in asthmatic subjects remain to be explored.

We have also shown that SO_2 exposure causes ciliary damage in nasal epithelial biopsies from human subjects. Surprisingly, exposure to O_3 did not appear to cause similar defects (Carson et al, 1985).

Thus the Cooperative Agreement has supported a body of collaborative research that has had important impact on our knowledge and understanding of the effects of controlled exposure to criteria air pollutants on normal humans and on a variety of well-characterized subpopulations. This information is generally recognized as contributing significantly to regulatory thinking within the Agency. Among the scientific community, there is no doubt that the scientific reputation of the Clinical Research Branch has been enormously enhanced.

To examine the issue of whether the research being conducted at the Clinical Research Branch has kept pace with developments in modern biological research, especially as they apply to lung biology, several points can be made:

1) We have developed nasal and broncho-alveolar lavage procedures to obtain material suitable for studies of lung cell biology in relation to inhalational toxicology. These procedures are now being used on an almost daily basis for a variety of protocols.

2) As previously noted, we have developed cultured cell systems and methods of exposing such surfaces to gaseous substances. We have studied respiratory epithelial cells, pulmonary vascular endothelial cells and pulmonary alveolar macrophages. We have developed evidence of dose-related ozone effects on arachidonate metabolism of endothelial cells and alveolar macrophages.

3) We have applied new technologies to examine respiratory epithelial function and its cellular basis in relation to inhalational toxicology as well as infections. We have established a morphology laboratory that performs sophisticated studies of respiratory structures in tissues obtained from human as well as animal sources.

4) We have developed an animal model (the outbred Blo/Y mouse) to study the effects of air pollutants on lung collagen and elastin. We have developed sensitive immunoassays for fragments of elastin and collagen for application to studies of acute lung injury.

5) We have provided essential support in the form of space, equipment and professional personnel to the development of CRB programs in lung cell biology and in particle deposition, detection and clearance.

6) We have made major steps in developing an indoor air pollution study program, with particular emphasis on health effects in children.

In supporting these developments, we have not neglected the more classical areas of respiratory physiology, including gas exchange and mechanics and have instituted important testing procedures such as multigas rebreathing and random-noise oscillation. We are currently studying the potential of NMR techniques for refined imaging studies, investigation of lung metabolism, and quantitation of mucociliary clearance.

Finally, in terms of recruitment and retention of productive scientists: The Cooperative Agreement has been directed since its inception by Dr. Philip

Bromberg, Professor of Medicine and Chief of the Division of Pulmonary Medicine, and by Dr. Albert Collier, Professor of Pediatrics and Chief of the Division of Pediatric Infectious Diseases. These individuals have not only devoted major fractions of their time and effort to the Cooperative Agreement, they have stimulated members of their own divisions to develop research relevant to the needs of the CRL and to collaborate more widely within the HERL. They have been widely recognized in the scientific community as leaders in the area of air pollution.

Through their efforts a number of major project leaders have been recruited among the University faculty. These include:

M. J. Hazucha, MD, PhD (Environmental Inhalation Toxicology)
Research Associate Professor of Medicine
(Inhalational Toxicology and Applied Physiology)

V. Ranga, MD
Assistant Professor Medicine (deceased, 1985)
(Inhalational Toxicology and Experimental Lung Pathology)

M. Friedman, MD
Associate Professor of Medicine
(Pulmonary Vasculature, Toxicology of Endothelium)

B. Boehlecke, MD, MSPH (Epidemiology)
Associate Professor of Medicine
(Inhalational Toxicology, Respiratory Physiology, Bronchoscopy and Lavage)

D. Sheps, MD
Associate Professor of Medicine
(CO and Ischemic Heart Disease)

K. Adams, MD
Assistant Professor of Medicine
(Nuclear Cardiology; CO and Heart Disease)

F. Henderson, MD
Associate Professor of Pediatrics
(Ozone and Experimental Respiratory Viral Infection)

J. Carson, PhD (Botany)
Assistant Professor, Pediatrics, Anatomy and Cell Biology
(Lung Ultrastucture)

P-C Hu, PhD (Microbiology and Immunology)
Associate Professor, Pediatrics, Microbiology & Immunology
(Immunoassay techniques)

M. Leigh, MD
Assistant Professor, Pediatrics
(Experimental exposures of Children)

M. Henry, MD
Assistant Professor of Pediatrics
(Experimental Lung Pathology)

G. Strope, MD
Associate Professor of Pediatrics
(Pulmonary Function in Children)

G. Mechanic, PhD (Chemistry, Biochemistry)
Professor of Biochemistry
(Lung collagen and elastin)

L. Kwock, PhD (NMR Spectroscopy; Cell Biology)
Associate Professor of Radiology
(NMR Techniques)

P. Reist, PhD
Professor of Environmental Sciences & Engineering
(Particle Deposition)

D. Leith, PhD
Professor of Environmental Sciences & Engineering
(Particle Generation/Deposition)

W. McCartney, MD
Associate Professor of Radiology
(Cardio-pulmonary Imaging)

G. Koch, PhD (Statistics)
Professor of Biostatistics
(Study design, analysis)

J. Fullton, MS (E.Eng.)
Research Associate, Medicine
(Applied physiology, Computer interfacing)

D. Harris, PhD (Immunobiology)
Research Associate
(Immunology)

W. Kozumbo, PhD (Biochem. Toxicology)
Research Associate
(Toxicology, Carcinogenesis)

In terms of EPA scientists whose recruitment and work has been influenced and supported in major fashion by the Cooperative Agreement, it seems appropriate to mention in particular:

Hillel Koren, PhD, Chief, Cell and Molecular Biology Section, CRB
(Adjunct Professor, Microbiology & Immunology, UNC School of Medicine)

R. Devlin, PhD, Member of Cell and Molecular Biology Section, CRB
(Adjunct Assistant Professor of Biochemistry, UNC School of Medicine)

T. Gerrity, PhD, Chief, Aerobiology Section, CRB
(Adjunct Associate Professor of Medicine, UNC School of Medicine)

H. Kehrl, MD, Medical Officer, CRB

It should be pointed out that much of the equipment used by Dr. Gerrity's and by Dr. Koren's sections (see Appendix 2) and much of Dr. Koren's space (Appendix 3) has been provided by UNC through the Cooperative Agreement.

Construction funds were used for two major purposes:

1. Renovation of laboratory and office space in Medical Building B assigned by the School of Medicine to the CEM. This space ~ 3,500 sq ft) has been allocated to members of the CEM and scientists and technicians in the Cell and Molecular Biology Section of the Clinical Research Branch directed by Dr. Hillel Koren. All these scientists work in a close collaborative relationship. Additional funds were used to improve access between Medical Building C which houses the principal research facilities of the Clinical Research Branch (and is leased from UNC by HERL/EPA) and Medical Building B.

2. Purchase of a 1400 sq ft mobile unit sited adjacent to Medical Building C and used to house offices for CEM core scientists and staff, offices for EPA scientists and staff, and a common computer facility designed to provide information search and graphics capabilities. The development of this additional space was an urgent necessity when the occupancy of Medical Building C had to be reduced for safety reasons.

Both of these projects are designed to maintain and enhance the closest possible contact between EPA and CEM scientists and supporting personnel.

In addition the Cooperative Agreement has supported at least three post-

doctoral fellows each year (see Appendix 3) who have worked at the CRB under the supervision of EPA scientists and of UNC faculty. The work performed by these trainees has been and continues to be invaluable in helping the CRB fulfill its mission. Indeed, one of these trainees (Dr. H. Kehrl) has become a staff scientist at the CRB.

Thus, we believe that in all the following aspects:

1. development of fruitful interactions between UNC and EPA staff
2. scientific productivity
3. enhancement of the scientific reputation of the CRB
4. broadening of its scientific base
5. recruitment of scientists
6. training
7. scientific enrichment

the Cooperative Agreement has amply fulfilled its objectives. The UNC Center for Environmental Medicine looks forward to a continuing close association with multiple laboratories within HERL, and particularly with the CRB. We believe that this association will continue to be of the greatest value to both partners, and that it will constitute a model for successful interaction between a public university and a federal agency in the area of biological and clinical research.

APPENDIX 1

1981

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APPENDIX 2

CENTER FOR ENVIRONMENTAL MEDICINE
EQUIPMENT PURCHASED COSTING MORE THAN $1,000
THROUGH US EPA COOPERATIVE AGREEMENT
CR 807392 FROM 8/11/80 to 12/31/86

	Item	Fiscal Year Acquired	Total Cost
1.	Chromatograph Data Mod 730 SN 1757-4467	1982	5,408
2.	Microscape Microstar ML AO-DX H110BU-F	1982	3,045
3.	Tissue Processor ML 4640-B SN Y3911-34	1981	3,525
4.	Balance Sartorius SN 3312271	1984	1,450
5.	Diamond Knife Microstar SN 1330	1984	1,726
6.	Microtome Allied JB4 SN 84026	1986	7,496
7.	Microtome AO 820 SN 67904	1981	2,162
8.	Histo Center	1981	1,978
9.	Microtome Knife Sharpener ML 903 SN 1271	1982	1,625
10.	High Vacuum Freeze Unit ML BA F400T SN P02004-544	1982	71,733
11.	Container Liquid Nitro ML LS-160 SN 010-185-P5	1983	1,349
12.	Ultratome LKB SN 285	1983	10,920
13.	Power Supply ML PS500X SN 84181	1985	1,686
14.	Spinning Top Aerosol Generator R 38125 SN 3165-181	1985	7,132
15.	Word Processor CPT ML 8515 SN 228416A	1984	6,215
16.	Terminal Graphic Ramtek ML 6211 SN 5653072	1983	6,600
17.	Word Processor CPT ML 8525 SN 211541	1983	13,362

18.	Computer IBM AT 5170 SN 0094955	1986	5,396
19.	Ergometer Table ML 846T SN 01-59-002-553	1982	9,129
20.	Bicycle Pedalmate	1983	4,670
21.	Monitor Holter Oxford ML MR-14 SN 51564	1983	2,070
22.	ECG Machine Marquette ML MAC S-A SN C4M403895	1984	17,940
23.	Printer Digital ML LA100-PC SN 80771	1984	1,158
24.	Computer Digital Rainbow PC 1-00-A SN WF52323	1984	3,522
25.	Printer IBM Quietwriter 5201 SN 0117429	1986	1,020
26.	Printer C ITOH ML F10-40 SN 024078	1983	1,938
27.	Microscope Olympus ML IM SN 101648	1983	3,000
28.	Liq Scintillation Counter LKB SN 1153	1985	17,765
29.	Printer LKB for RA CK Beta SN 3440696	1985	1,045
30.	Display Terminal LKB SN 41400	1985	1,045
31.	Spectrum Analysis Unit LKB 4420 SN 411-0293	1985	4,964
32.	Microscope A-O Trinoc SN 233824	1983	1,982
33.	Water bath refrig lab ML 2006 SN 2007321	1983	1,219
34.	Gamma Counter Packard ML B5301 SN 34870	1984	14,040
35.	Computer IBM PC 5150 SN 0693661	1985	2,761

36.	Bronchofiberscope ML BF-1TR SN 212051	1983	7,197
37.	Incubator Bellco Glass SN 3B-04	1982	1,526
38.	Cabinet Bio Safety Hood MLNU408RM3 00 SN 5919NU	1983	3,692
39.	Stand Microscope Opelco ML 1M T2	1985	4,063
40.	Computer IBM XT 5160 SN 6103418	1986	2,000
41.	Basic FACS Analyzer System w/ wide angle light scatter detector module including photomultiplier tube and analog processing electronics	1985	60,349
42.	Climet Optical Particle Counter Model CI-208C; Printer, Model 99000153; histogram display	1984	10,040
43.	Wet Test Flow Meter	1984	1,709
44.	Digital Pressure Manometer	1984	1,757
45.	ACFM Abient Impactor	1984	3,185
46.	Double-wide Modular Facility	1985	30,094
47.	LKB 1217D802 RackBeta III LSC 300	1984	23,959
48.	Chilled Water Recirculator	1984	2,536
49.	Starwriter F-10 40 CPS	1982	1,449
50.	Climet Optical Particle Counter w/printer & histogram display	1984	9,550
51.	Canberra Multi-channel Analyzer	1984	5,191
-			
		Total	410,373

APPENDIX 3

Post-Doctoral Fellows Supported by US EPA Cooperative Agreement CR 807392

Benu Chatterjee, MD

David Davin, MD

Mark Ivanick, MD

Howard Kehrl, MD

William Mentz, MD

Penelope Muelenaer, MD

John M. Price, MD

Robert Schreiber, MD

Jeffery Dale Sargent, MD

Steven Turker, MD

Robert Vender, MD

Robert Vorona, MD

Karen Voter, MD

Paul Weinberg, MD

APPENDIX 4

1983

Dr. Ted Martonen became a consultant to the Center involved with developing models of uptake and deposition of inhaled air pollutants and specifically with aerosolized particle behavior in biologic systems, in January, 1983.

Dr. Gerard Huchon from Hopital Laennec, Paris, France presented a seminar entitled "In vivo studies of human epithelial permeability in health and disease measured with the gamma camera,"in May 13, 1983.

Dr. Michael Kleinman, Department of Community and Environmental Medicine, University of California at Irvine, California, presented a seminar entitled "Controlled Human and Laboratory Animal Exposures to Complex Air Pollutant Mixes,"in May 26, 1983.

Dr. Donovan Yeates, Section of Environmental Medicine, University of Illinois, Chicago, Illinois, presented a seminar entitled "Deposition and Clearance of Inhaled Particles in Humans and Animals," in June 23,1983.

Dr. William S. Beckett, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, presented a seminar entitled "Exercise and Thermal Regulation Following Prolonged Bed Rest in Normal Women,"on July 5, 1983.

Dr. David Johnson, East Tennessee State University, presented a seminar entitled "Inactivation of Protease Inhibitors by Oxidants," on July 15, 1983.

Dr. Allen Cooper, Pulmonary Division, Yale University, New Haven, Connecticut, presented a seminar entitled "Role of Lymphocytes in the Lung Response to Toxic Materials,"on September 6, 1983.

Dr. Morton Lippmann, Department of Environmental Medicine, New York University, presented a seminar entitled "Use of Aerosols for Measuring Functional Responses in Humans to Inhaled Pollutants," on September 15, 1983.

Gary Hunninghake, MD, Director, Pulmonary Disease Division, Department of Internal Medicine, University of Iowa, Iowa City, Iowa, presented a seminar entitled "Use of Bronchoalveolar Lavage," on November 9, 1983.

John Clements, MD, Director, Lung Metabolism Laboratory, University of California School of Medicine, Cardiovascular Research Institute, San Francisco, California, presented a seminar entitled "The Role of Surface Active Material in Lung Disease," on December 6, 1983.

Eugene Rannels, MD, Department of Physiology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Penn, presented a seminar entitled "Pulmonary Metabolism of 5-hydroxytryptamine: Effects of altered Flow and Ventilation and of anesthetic exposure," on January 10, 1984.

Jerome Kleinerman, MD, Chairman, Department of Pathology, Mount Sinai Medical Center, New York, NY, presented a seminar entitled "Injury and Repair in the Lung Following Prolonged NO_2 Exposure," on February 1, 1984.

Gareth Green, MD, Chairman, Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, MD, presented a seminar entitled "Pulmonary Infection and Immunity," on March 7, 1984.

Keith Tanswell, MD, Department of Pediatrics, St. Joseph's Hospital, Ontario, Canada, presented a seminar entitled "Antioxidant Enzyme Activity in Rat Fetal Lung In vitro and In vivo," on April 11, 1984.

David V. Bates, MD, Professor of Medicine from the University of British Columbia, Vancouver, B.C., visited the Center doing preparatory work for his fall sabbatical at the U.S. EPA facility in Chapel Hill from April 16-20, 1984.

George J. Jakab, MD, Department of Environmental Health Sciences, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland presented a seminar on May 29, 1984.

Malay K. Mazumber, PhD, Professor and Head of the Department of Electronics and Instrumentation at the University of Arkansas, Graduate Institute of Technology, and Research Associate J. Douglas Wilson, presented a seminar on July 18 and consultd with staff members on July 19, 1984.

David V. Bates, M.D., Visiting Distinguished Professor, University of British Columbia, Vancouver, Canada, presented a seminar entitled "Chronic Obstructive Lung Disease" on October 3, 1984.

Allan M. Ross, M.D., Professor of Medicine at the George Washington University Medical Center in Washington, D.C., consulted on the carbon monoxide project with Dr. David Sheps and EPA personnel on October 29 and 30, 1984.

Jere Mead, MD, Department of Physiology, Harvard University, Boston, Mass, presented a seminar entitled "Expiratory Flow Limitation: A Physiologist Point of View, Parts I and II," on October 31 and November 1, 1984.

Aaron Janoff, Ph.D., Department of Pathology, State University of Stonybrook, New York, presented a seminar entitled "Cigarette Smoking versus Protease and Antiprotease homostasis in the Lungs," on December 5, 1984.

Peter A. Valberg, PhD, Associate Professor of Physiology at the Harvard School of Public Health in Boston, Massachusetts, conducted a seminar on November 8, 1984, entitled "Macrophage Function Evaluated Using Magnetic Aerosols."

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Lawrence Lichtenstein, MD, Johns Hopkins University School of Medicine, Baltimore, MD, presented a seminar entitled "In Vitro Studies of Purified Human Basophils and Mast Cells," on January 9, 1985.

Timothy R. Gerrity, PhD,Research Assistant Professor of Medicine at the University of Illinois at Chicago, conducted a seminar on January 15, 1985, entitled "Disrupting Lung Muccociliary Clearance."

Philip Sannes, PhD, Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, MD, presented a seminar entitled "Pulmonary Basement Membranes: A Cytochemical Perspective," on February 6, 1985.

Haim Ginsburg, Ph.D., of the Rappaport Family Institute for Research in Haifa, Israel, conducted a seminar on February 13, 1985 entitled "Granular Natural Killer Cells Develop into Mucous Secreting Cells."

Barry T. Smith, MD, Departme t of Pediatrics, Harvard Medical School, Boston, Mass. presented a seminar entitled "Febroblast-Pneumonocyte Facter: Future Clinical Role," on March 6, 1985.

Timothy R. Gerrity, PhD, Department of Medicine, University of Illinois, Chicago, Illinois, was a consultant to the Center on the details of establishing a particle physics laboratory from April 1-5, 1985.

Martino Introna, PhD, Research Associate, Department of Medicine, Duke University, presented a seminar entitled "Suppressive Activity of Human Alveolar Macrophages" on May 21, 1985.

Dr. Richard A. Berg, Associate Professor of Chemistry, Rutgers Medical School, Department of Biology, Piscataway, NJ presented a seminar on Tuesday, July 2, 1985 entitled "Oxygen Toxicity in the Rat Lung: A Model for Emphysema."

Allan M. Ross, MD, The George Washington Univ. Medical Center, Washington, DC was a consultant on the carbon monoxide project with Dr. Sheps and EPA personnel on July 31, 1985.

Lynne Reid, MD, S. Burt Wolbach Professor of Pathology and Chairman, Department of Pathology, Harvard Medical School, Boston, Mass, presented a seminar entitled "Pulmonary Hypertension - Restrictive no Constrictive," on October 2, 1985.

John McDonald, MD, Assoc. Prof of Medicine, Asst. Prof of Biochemistry, and Director of the Pulmonary Disease Division, Washington University School of Medicine, St. Louis, Mo, presented a seminar entitled "Fibronectins - Adhesive Glycoprotein Organizers of the Pericellular Matrix," on November 6, 1985.

Frances Silverman, PhD, The Gage Research Institute, Toronto, Canada presented a seminar entitled "Recent Studies of the Effects of Environmental Factors on Asthmatics," on November 14, 1985.

Robert Devlin, PhD, Department of Biology, Emory University, Atlanta, Georgia presented a seminar entitled "Developmental Regulation of Tropomyosin Gene Expression by Alternative Splicing" on November 27, 1985.

Alfred P. Fishman, MD, University of Pennsylvania Department of Medicine and Director, Cadiovascular-Pulmonary Division, Hospital of the Univ. of Penn, Philadelphia, PA presented a seminar "Water and macromolecular exchange function of the Lungs," on December 4, 1985.

Yona Keisari, PhD, Department of Human Microbiology, Tel Aviv University, Israel, presented a seminar entitled "Macrophage Oxidative Burst and Related Phenomena," on December 11, 1985.